

This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

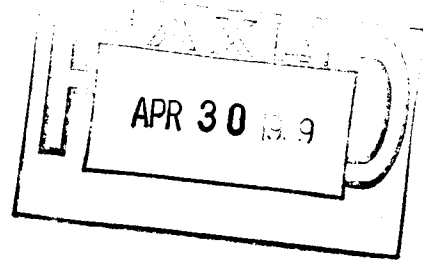


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April 30, 1999

Via Facsimile

Ms. Pam Noyes
Special Review and Reregistration Division
Office of Pesticide Programs
United States Environmental Protection Agency
Mail Code 7508W
401 M Street, S.W.
Washington, D.C. 20460



Re: DDVP

Dear Pam:

Appended, as promised in my letter to you dated April 22, 1999, is Amvac Chemical Corporation's interim submission. The topics covered are:

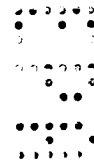
- Animal Studies Measuring the Health Effects of Repeated Exposure to DDVP Vapor, Blair, *et al.*; and
- Sensitive Sub-Populations and Inter-individual Variability: Dichlorvos EPA Draft Risk Assessment Literature Not Mentioned.

Please remember that this is an interim document. Although the greatest care has been taken with preparing its content, there is always the possibility that as the full document is completed, additional data will be reviewed that may affect the stated conclusions. Amvac thus reserves the right to change any of the conclusions under these circumstances. Please note that the term "additional data" only includes data that have already been submitted to EPA.

As always, please call with any questions.

Sincerely,

Ian S. Chart



Attachments

cc: Marcia E. Mulkey, Esquire (w/attachments)
Mr. Robert C. McNally (w/attachments)
Mr. Jack E. Housenger (w/attachments)
Mr. Dennis Utterback (w/attachments)

Animal Studies Measuring the Health Effects of Repeated Exposure to DDVP Vapor

BLAIR, D., ET AL. "2-YEAR INHALATION CARCINOGENESIS STUDY IN RATS." *ARCH. TOXICOL* 35:281-294.

The Blair and Stevenson study was designed as a 2-year inhalation carcinogenesis study in rats. An unusual strain of rats, the Carworth farm E strain rat, was utilized and the animals were bred under conditions that were specific pathogen free at the Tunstall Laboratory. Technical dichlorvos of greater than 97% purity was utilized. Groups of 50 rats of each sex were housed individually in metal cages and placed in inhalation chambers. Dichlorvos vapor was generated and measured daily. Exposure persisted for at least 23 hours per day. Food and water was available ad-lib and changed weekly. Because the exposures were whole body, it is not known what the relative proportion of DDVP exposure was received via the inhalation route versus the dose from skin absorption, ingestion from preening, and ingestion from the continuous exposure of the food and water to DDVP vapor. Estimates by the author were that the inhalation dose was one-half to one-seventh of the total dose.

At the end of the 2-year study, the surviving animals were killed; blood samples taken for analysis of RBC and plasma cholinesterase, and the animals were necropsied. The left half of each brain was used for measurement of cholinesterase activity.

During the study, there was a treatment-related decrease in body weight that was noticeable in the highest dosage group (5.0 mg/m³) and an increase in survival in the DDVP exposed animals. The following summarizes the survival at the end of the 2-year study.

Survival of rats at the end of the 2-year inhalation study of Blair *et al.*

Exposure Group mg/m ³	Number surviving 2 years
Control males	8
0.05	18
0.5	12
5	29

Exposure Group mg/m ³	Number surviving 2 years
Control females	18
0.05	24
0.5	23
5	31

No difference in the incidence of tumors among the treated and control groups was apparent.

Pretest measurements of either RBC or plasma cholinesterase were not made. No measurements of cholinesterase were made during the study in the study animals. Therefore, the only analysis of RBC and plasma cholinesterase possible was to compare the values obtained to those in the control group. The following is a summary of the cholinesterase values obtained in the terminal analyses.

**Cholinesterase values of rats surviving the 2-year exposure to DDVP
(micro moles) ml⁻¹ min⁻¹ and percent of control activity ()**

Exposure Group mg/m ³	Plasma ChE	RBC ChE	Brain ChE
Control males	1.02	0.99	12.13
0.05	0.98 (96)	0.99 (100)	11.64 (96)
0.5	0.78 (76)	0.71 (72)	10.93 (90)
5	0.38 (38)	0.04 (4)	2.51 (21)

Exposure Group mg/m ³	Plasma ChE	RBC ChE	Brain ChE
Control females	1.82	1.28	11.28
0.05	1.68 (92)	1.13 (88)	10.90 (97)
0.5	1.52 (84)	0.88 (69)	10.10 (90)
5	0.40 (22)	0.07 (5)	2.13 (19)

CONCLUSIONS:

In Carworth farm E strain rats, RBC cholinesterase is the most affected by treatment with DDVP. Even though in the 5 mg/m³ dosage groups, the RBC cholinesterase was less than 5% of controls, no signs of cholinesterase toxicity was apparent in any of the animals. Likewise, when brain cholinesterase is inhibited to only 20% of control values, no signs of clinical effects were apparent. Levels of 0.5 and 5 mg/m³ were considered

effect levels and 0.05 mg/m³ was the no effect level. No evidence of carcinogenicity was apparent at any site. The dose the animals received is the sum of the inhaled dose plus the dose from preening, skin absorption, and ingestion of contaminated food and water. Even though the contribution of DDVP exposure from non-inhaled sources was estimated by the authors as substantial, EPA ignored other routes of exposure in their dose estimate.

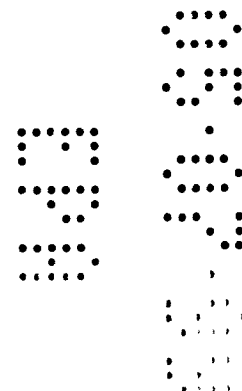
This study is not a good study on which to base the NOAEL for chronic inhalation exposure to DDVP for the following reasons:

1. The dose the animals received is unknown but is substantially in excess of the dose estimated from only inhalation of 0.05mg/m³ of dichlorvos vapor.
2. The effects on cholinesterase cannot be assumed to be from only the inhaled dose.
3. The strain of rats is unusual and it is not known if their cholinesterase response is atypical.
4. Cholinesterase measurements were only made at the end of the animal's lifespan and there is uncertainty about whether these surviving rats are typical or not of normal adult rats.
5. There is no information about the time course for cholinesterase inhibition.
6. Because cholinesterase measurements were not made during the study or pretest, comparisons were limited to the control group.
7. Survival was increased by DDVP, therefore an unequal number of animals was available for measurements.
8. Because RBC cholinesterase is affected most in these rats, we know the response to DDVP in this strain of rats is not similar to that in humans.

Blair, et al.:

1) Study Strengths:

- a) Exposure duration long.
- b) Exposure measurements reported in detail.
- c) Exposure methods discussed in detail.
- d) Range of exposures over more than 10-fold studied.
- e) Relatively high levels of exposure to DDVP studied.



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- f) Statistical analysis and variability reported.
- g) Obtained brain cholinesterase measurements.

2) Limitations:

- a) Dose estimation difficult. Total dose is the sum of the inhalation exposure plus additional DDVP exposure from preening, skin absorption, and ingestion from food and water contamination.
- b) Chronic cholinesterase measurement not the purpose of the study.
- c) Unusual strain of rat utilized.
- d) Lack data on cholinesterase levels in these rats at this age for comparison.
- e) No pretest measurements for comparison of ChE.
- f) Cholinesterase measured only once at the end of their lifetime on geriatric rats.
- g) DDVP prolonged life, confounding the number of animals tested for ChE.
- h) The measured sensitivity of RBC cholinesterase is not like the response in humans.
- i) Extrapolation to man uncertain.

Selection of the Best Study to Serve as the Basis for the Repeat Inhalation Risk Assessment of Dichlorvos

Study Type	Animal Study	Human Studies	
Study	Blair, <i>et al.</i> (1976)	Funckes, <i>et al.</i> (1963)	Leary, <i>et al.</i> (1974)
Citation	Shell Chemical Co. report & publication	WHO Study	Shell Chemical Co. report & publication
Purpose	Carcinogenicity	Cholinesterase effects and health observations	Cholinesterase effects/health observations & food exposures
Species	Rats	Humans	
Population Tested	Carworth farm E strain	Men, women, and children	
Age	Geriatric rats, those surviving 2 years	4 months to 64 years	
Number Tested	8 to 24	19 selected randomly 25 additional 11 other children (ave. 23 mo.)	7 adults and 11 children
Exposure Route	Vapor	Vapor	Vapor
DDVP Source	Vapor generator	Vapor from solid source	8 to 18 pest strips per home
Other Routes	Preening off fur, deposition in food, water, skin	Possibility for skin, food	Food exposures exaggerated with pest strips added to kitchen and dining room
Setting	Chambers	Homes in Africa kept closed all evening and at night	Homes in Arizona kept closed
Schedule	23 hours/day	Continuously inside home	Continuously inside home
Days per Week	7	7	7
Length of Exposure	2 years	7 weeks	44 days
ChE Determinations	1	1 to 4 each	3 prior to exposure 13 during exposure

Analysis	Compared to controls	Compared to pretest values
NOAEL	0.05 mg/m ³	0.43 mg/m ³
Supporting Data	Little	1) Other WHO studies, 2) Kettering Lab., 3) Ottevanger
Uncertainty	High	Low to medium
Extrapolation	Difficult	Easy

1) Blair, D., *et al.* (1976). "2 Year Inhalation Carcinogenesis Study in Rats." *Arch. Toxicol* 35:281-294.

2) Funckes, AJ, *et al.* (1963). "Initial Field Studies in Upper Volta with Dichlorvos Residual Fumigant as a Malaria Eradication Technique." *Bull Wld Hlth Org.* 29:243-246.

3) Leary, JS, *et al.* (1974). "Safety Evaluation in the Home of Polyvinyl Chloride Resin Strip Containing Dichlorvos (DDVP)." *Arch Environ Health* 29:308 - 314.

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Sensitive Sub-Populations and Inter-individual Variability

Dichlorvos EPA Draft Risk Assessment Literature Not Mentioned

Cavagna, G., G. Locali, and E.C. Vigliana (1969). "Clinical effects of exposure to DDVP (Vapona) insecticide in hospital wards." *Arch. Environ. Health* 19:112-123.

This study measured plasma and RBC cholinesterase in sick adults and children exposed to pest strips continuously in hospital wards. Patients in a hospital were exposed to DDVP from resin strips with a maximum level of 0.28 mg/m^3 (range of 0.1 to 0.28 mg/m^3). There was no effect on RBC cholinesterase in any group.

The following groups showed no effect on plasma or RBC cholinesterase:

- 29 women continuously during labor through 5 days post-partum;
- 4 sick men exposed continuously for 3 to 16 days to concentrations between 0.02 and 0.1 mg/m^3 ;
- 17 sick men exposed 16 hours per day for 3 to 16 days to concentrations between 0.1 and 0.28 mg/m^3 ;
- 40 sick men exposed 16 hours per day for 3 to 16 days to concentrations between 0.02 and 0.1 mg/m^3 ;
- 8 sick children (ages: 2 to 7 years old); and
- 5 sick babies (ages: 7 to 21 months old).

Slight to moderate decreases in plasma cholinesterase were noted in:

- 5 sick men exposed at concentrations above 0.1 mg/m^3 ;
- 6 men with severe liver disease (0.1 to 0.22 mg/m^3); and
- 11 sick babies (ages: 7 to 21 months old) exposed to concentrations above 0.1 mg/m^3 .

Cavagna, G., G. Locali, and E.C. Vigliana (1970). "Exposure of newborn babies to <<Vapona>> insecticide." *European J. Toxicol.* III:49-57.

This study measured cholinesterase levels in plasma and RBC of newborn babies exposed for the first 5 days of life continuously to the vapors from pest strips in ventilated and poorly ventilated conditions. Sixty-nine healthy newborn babies were exposed to DDVP vapors from resin strips for five days. The maximum concentration was 0.128 mg/m^3 with a mean of 0.053 mg/m^3 . A second study had

a maximum air concentration of 0.28 mg/m³ with a TWA of 0.15 mg/m³. There was no difference in plasma and red blood cell cholinesterase values.

Pena Chavarria, A., J.C. Swartzwelder, V.M. Villarejos, E. Kotcher, and J. Arguedas (1969). "Dichlorvos, an effective broad - spectrum anthelmintic." *A. J. Trop. Med. Hyg.* 18(6):907-911.

Various health measurements were made on 108 hospitalized male and female adults, aged 16 to 75, with clinical manifestations of intestinal parasite infections. Fifty-one males and 57 females participated in the study. Many of the patients were seriously anemic and debilitated from their disease. Two groups were dosed with slow-release, granular-resin formulated DDVP in either a single oral dose of 6 or 12 mg/kg body weight. Cholinesterase levels in plasma and RBC were measured before and after administration of DDVP. There were no clinical side effects observed in the patients, with the exception of a few brief, mild headaches. Reduction in plasma cholinesterase lasted from 24 to 72 hours before returning to pretreatment levels. No symptoms associated with organophosphate toxicity (e.g., vomiting, gastric hypermotility, or increased salivation) were present in any of the 108 patients, however. More than 50% of patients were cured with the single 6 mg/kg dose and more than 75% patients with the single 12 mg/kg dose were cured.

Cervoni, W.A., J. Oliver-Gonzalez, S. Kaye, and M.B. Slomka (1969). "Dichlorvos as a single-dose intestinal anthelmintic therapy for man." *A. J. Trop. Med. Hyg.* 18(4):912-919.

A very large population of 705 adults in rural Puerto Rico, all of whom were ill with intestinal parasites (*i.e.*, Trichuris, hookworm, or Ascaris, or all three), were given slow-release formulations of DDVP up to 12 mg/kg. The health of the individuals was monitored and both plasma and RBC cholinesterase measurements were made. No clinical symptoms were noted after exposure to DDVP. No changes were seen in kidney or liver function. There was no change in RBC cholinesterase levels. The decreases in plasma cholinesterase were designated as "little-to-modest." The plasma cholinesterase levels returned to pretreatment levels within one week of treatment. The treatment was considered safe and effective, with a unique effectiveness against the whipworm (*Trichuris*).

Uchiyama M., T. Kawakami, and H. Hiuga (1967). "Effect of Vapona Strips to human beings and the method of determination of DDVP concentration in the air." *Pharmaceutical Dept., Faculty of Medicine, Tohoku University*.

This study measured cholinesterase levels in seriously ill children aged 4 months to 2 years 8 months who were exposed continuously up to 3 months in hospital rooms with pest strips. Measurements were made in a room with air conditioning and in a room without air conditioning. Three Vapona strips were hung in a Pediatrics ward of 93 m³. No effects were observed on the plasma cholinesterase levels.

Also, similar cholinesterase measurements were made of twenty hospitalized adults with a variety of illnesses that were continuously exposed to pest strips for up to 72 days. Four strips were hung in an adult ward of 120 m³. No effects were observed on the plasma cholinesterase levels.

Tracy, R.L., J.G. Woodcock, and S. Chodroff (1960). "Toxicological aspects of 2,2'-dichlorovinyl dimethylphosphate (DDVP) in cows, horses, and white rats." *J. Econ. Entomol.* 53(4):593-601.

This study measured cholinesterase levels after administration of doses of DDVP sufficient to cause severe cholinesterase inhibition in cows and rats. The levels of cholinesterase in the suckling young were normal. Additionally, five horses exposed continuously for 22 days to air levels ranging between 0.24 and 1.48 mg/m³ DDVP showed no effects on plasma cholinesterase.

CONCLUSIONS

These studies provide information on the effects of DDVP exposure on varied subpopulations. There were no clinical signs attributable to DDVP exposure. No effects were seen on RBC cholinesterase levels for either adults or children regardless of their health status. Additionally, effects on plasma cholinesterase levels were minimal even for very sick patients exposed to DDVP levels in excess of those seen following typical

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use. These data provide assurance of the safe use of DDVP resin strips under typical use conditions regardless of the population types exposed.